Efficacy and Safety of Alirocumab in Individuals with Diabetes Mellitus

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ORIGINAL RESEARCH

Efficacy and Safety of Alirocumab in Individuals with Diabetes Mellitus: Pooled Analyses from Five Placebo-Controlled Phase 3 Studies

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ABSTRACT

Introduction: Diabetes mellitus (DM) carries an elevated risk for cardiovascular disease. Here, we assessed alirocumab efficacy and safety in people with/without DM from five placebo-controlled phase 3 studies.

Methods: Data from up to 78 weeks were analyzed in individuals on maximally tolerated background statin. In three studies, alirocumab 75 mg every 2 weeks (Q2W) was increased to 150 mg Q2W at week 12 if week 8 low-density lipoprotein cholesterol (LDL-C) was ≥ 70 mg/dL; two studies used alirocumab 150 mg Q2W throughout. The primary endpoint was percentage change in LDL-C from baseline to week 24.

Results: In the alirocumab 150 mg pool (n = 2416), baseline LDL-C levels were 117.4 mg/dL (DM) and 130.6 mg/dL (without DM), and in the 75/150 mg pool (n = 1043) 112.8 mg/dL (DM) and 133.0 mg/dL (without DM). In the 150 mg Q2W group, week 24 LDL-C reductions from baseline were observed in persons with DM (− 59.9%; placebo, − 1.4%) and without DM (− 60.6%; placebo, + 1.5%); 77.7% (DM) and 76.8% (without DM) of subjects achieved LDL-C < 70 mg/dL. In the alirocumab 75/150 mg group, 26% (DM) and 36% (without

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DM) of subjects received dose increase. In this group, week 24 LDL-C levels changed from baseline by − 43.8% (DM; placebo, + 0.3%) and − 49.7% (without DM; placebo, + 5.1%); LDL-C < 70 mg/dL was achieved by 68.3% and 65.8% of individuals, respectively. At week 24, alirocumab was also associated with improved levels of other lipids. Adverse event rates were generally comparable in all groups (79.8–82.0%).

Conclusions: Regardless of DM status, alirocumab significantly reduced LDL-C levels; safety was generally similar.

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Keywords: Alirocumab; Cholesterol-lowering drugs; Diabetes mellitus; LDL-C; PCSK9

PLAIN LANGUAGE SUMMARY

High cholesterol puts people at risk of heart disease, especially those with diabetes. Physicians set individualized cholesterol treatment goals for each patient. Statins, prescribed to reduce high cholesterol levels, may not lower cholesterol enough in all people. Alirocumab is a medication for lowering cholesterol levels. Alirocumab is intended for use in combination with maximally tolerated statin. Here we compared the effects of alirocumab to 1054 people with diabetes to 2445 people without diabetes.

Our study showed that most people with and without diabetes reached the cholesterol goal of less than 70 mg per deciliter after 24 weeks of treatment with individualized alirocumab doses. Treatment with alirocumab 150 milligrams every 2 weeks resulted in 78% of people with diabetes and 77% of people without diabetes reaching this goal. Treatment with alirocumab 75 mg every 2 weeks (with some individuals getting their dose increased to 150 mg) also produced similar results in people with diabetes (68%) and without diabetes (66%). Eighty percent of people with diabetes and 80% of people without diabetes had adverse reactions with alirocumab treatment. Similar rates of adverse reactions were reported in the corresponding placebo groups with diabetes (82%) and without diabetes (81%). Regardless of diabetes status, the most common adverse reactions among alirocumab-treated people were common cold, chest infection, and injection-site reaction.

In summary, alirocumab provides an additional treatment option for people with and without diabetes who do not to reach their cholesterol goals, even with maximally tolerated statin dose.

INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of death in persons with diabetes mellitus (DM) [1, 2]. Individuals with DM are, on average, at double the risk of atherosclerotic CVD (ASCVD) in comparison to those without DM, and the presence of dyslipidemia in people with type 2 DM further increases the risk of adverse cardiovascular outcomes [3, 4].

The elevated cardiovascular risk associated with DM is recognized in guidelines [1, 3, 5, 6], which recommend more intense management strategies for low-density lipoprotein cholesterol (LDL-C)-lowering in individuals with DM than for the general population. Statins are recommended as first-line therapy to reduce LDL-C in DM [1, 5, 7, 8]. However, many people with DM have persistent lipid abnormalities despite statin treatment [9, 10]. The 2017 updated American College of Cardiology Expert Consensus Task Force and the 2018 American Diabetes Association standards of care recommend that a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor be considered in individuals with ASCVD and DM whose LDL-C levels are not optimally controlled on high-intensity statin therapy [6, 8].

The 2017 update of the European Society of Cardiology/European Atherosclerosis Society Task Force also recommends the use of a PCSK9 inhibitor for two categories of individuals with DM, depending on LDL-C levels: (1) individuals with DM and clinical ASCVD whose LDL-C

levels are > 100 mg/dL and (2) individuals with DM and familial hypercholesterolemia without clinical ASCVD whose LDL-C levels are > 140 mg/dL, despite maximally tolerated statin and ezetimibe therapies [11].

The lipid profile of type 2 DM is characterized by reduced high-density lipoprotein cholesterol (HDL-C), high triglycerides, and an increase in the proportion of LDL-C particles that are small and dense, with or without high levels of LDL-C [12, 13]. In the ODYSSEY DM-INSULIN study (NCT02585778), alirocumab 75 mg every 2 weeks (Q2W; with possible dose increase to 150 mg Q2W) significantly reduced LDL-C levels and other lipids in individuals with type 1 DM (n = 76) or type 2 DM (n = 441) treated with insulin [14]. Furthermore, in individuals with type 2 DM and mixed dyslipidemia, the same alirocumab dosing regimen also resulted in significant reductions in non-HDL-C, LDL-C, and other lipids in ODYSSEY DM-DYSLIPIDEMIA (NCT02642159) [15]. However, the efficacy and safety of alirocumab 75 mg Q2W (with possible dose adjustment to 150 mg Q2W) and 150 mg Q2W (without dose adjustment) have not been compared in a larger pool of individuals with and without DM treated for longer duration. This subgroup analysis of five placebo-controlled phase 3 studies (LONG TERM [NCT01507831] [16], HIGH FH [NCT01617655] [17], COMBO I [NCT01644175] [18], FH I [NCT01623115] [19], and FH II [NCT01709500] [19]) aimed to compare the efficacy and safety of alirocumab in a large group of individuals with and without DM at baseline, with the primary efficacy endpoint being LDL-C reduction from baseline to week 24.

METHODS

Trial Participants and Study Designs

The current analysis used patient-level data from study participants according to alirocumab dosing regimen who enrolled for five double-blind, randomized, placebo-controlled ODYSSEY phase 3 studies with 52–78 weeks' treatment duration. Methods for each of the individual studies have been previously reported [16–19].

In summary, all participants, with or without DM, had hypercholesterolemia at study entry and were on maximally tolerated, stable, background statin therapy with or without other lipid-lowering agents. The FH I and FH II studies recruited participants with heterozygous familial hypercholesterolemia (HeFH) and at either very high risk (LDL-C ≥ 70 mg/dL with prior CVD) or high risk (LDL-C ≥ 100 mg/dL but no prior CVD). The HIGH FH study enrolled individuals with HeFH and LDL-C levels ≥ 160 mg/dL. The LONG TERM study included participants who either had HeFH or established coronary heart disease (CHD) or CHD risk equivalents based on the European Systematic Coronary Risk Estimation (SCORE), with baseline LDL-C ≥ 70 mg/dL. The COMBO I study included participants with either established CVD and LDL-C ≥ 70 mg/dL, or CHD risk equivalents and LDL-C ≥ 100 mg/dL, based on the European SCORE, which included DM with other risk factors or chronic kidney disease.

All study protocols were approved by the appropriate institutional review boards, and all participants provided informed, written consent. All trials were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and all applicable amendments laid down by the World Medical Assemblies and the International Conference Harmonisation Guidelines for Good Clinical Practice.

Participants were randomized to alirocumab or placebo groups in a 2:1 ratio. Two studies (LONG TERM and HIGH FH) used an alirocumab dose of 150 mg Q2W throughout the trial period. The other three studies (COMBO I, FH I, and FH II) used an initial alirocumab dose of 75 mg Q2W, with an increase to 150 mg Q2W at week 12 if the LDL-C level at week 8 remained ≥ 70 mg/dL. All doses were delivered by subcutaneous injection (alirocumab 75 mg, alirocumab 150 mg, or placebo) using a 1-mL dose volume.

Participants were classified as having DM (type 1 or 2) or not, according to medical history reported by the investigator.

Efficacy Analysis

Efficacy was compared in individuals with and without DM in two pools according to alirocumab dose regimen (pool of 150 mg Q2W studies; pool of 75 mg Q2W with possible increase to 150 mg Q2W, abbreviated in the text to 75/150 mg Q2W).

The main efficacy endpoint for this pooled analysis was the mean percentage change in calculated LDL-C from baseline to week 24 (the primary endpoint of the individual studies). Other efficacy endpoints included percentage change in calculated LDL-C from baseline to week 12 (prior to potential dose increase in trials utilizing the 75/150 mg Q2W dosing regimen), proportion of individuals achieving risk-based LDL-C goals, and the percentage change in other lipid parameters from baseline to weeks 12 and 24. Mean percentage change in LDL-C and other lipid parameters over time is also reported up to week 78.

Changes from baseline for the main LDL-C efficacy endpoint and other lipid values were statistically evaluated with an intention-to-treat (ITT) approach, which included lipid data from all randomized persons regardless of adherence to treatment. The analysis utilized a mixed-effect model with repeated measures to account for missing data, as previously described [20]. Data on changes over time were presented according to ITT analysis, and on-treatment analysis using a modified ITT approach, which included only lipid data collected while the individual was receiving study treatment.

Other lipid parameters were analyzed either in the same way as the main efficacy endpoint or, in the case of lipoprotein (a) [Lp(a)] and triglyceride (TG) percentage changes, and LDL-C goal achievement proportions, analysis involved a multiple imputation approach then robust regression (for Lp(a) and TG percentage changes) or logistic regression (for LDL-C goal achievement), in the ITT population.

Consistency of treatment effect across subgroups was assessed by providing interaction *p* values. A further subgroup analysis was performed to compare alirocumab efficacy in persons with and without DM according to HeFH status at week 12 and week 24.

Safety Analysis

Safety data are reported in subgroups of individuals assigned to alirocumab or placebo, regardless of alirocumab dose, according to baseline DM status. All adverse events, regardless of seriousness and irrespective of potential relationship to alirocumab, were recorded by the investigators up to the last visit planned in the protocol. Treatment-emergent adverse events (TEAEs) were defined as events that developed, worsened, or became serious between the first and last dose of study treatment plus 70 days, classified according to the Medical Dictionary for Regulatory Activities. Adverse events of special interest included injection-site reactions, general allergic events, neurocognitive disorders, and adjudicated cardiovascular events. Statistical analysis of the safety population included all randomized individuals who received at least one dose or part of a dose of study drug, and safety data were analyzed by descriptive statistics.

The effect of alirocumab treatment on glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) was also evaluated according to DM status throughout the studies using descriptive statistics conducted on the safety population.

RESULTS

Study Participants

In total, 30.1% of alirocumab-treated individuals ($n = 699$) and 30.2% of those receiving placebo ($n = 355$) were classified as having DM at baseline ($n = 1625$ and $n = 820$, respectively, were classified as not having diabetes) (Table 1; Supplementary Fig. 1). In total, 24 persons (0.69%) had type 1 DM and the remainder had type 2 DM. Individuals with DM were generally older and had a higher BMI versus those without DM. Fewer subjects with DM were male, white, or had HeFH compared with subjects without DM (Table 1). Fewer participants with DM had a history of ASCVD (62.5–62.8%) compared with those without DM (72.4–74.6%). Regardless of DM status, all

Table 1 Baseline demographics, clinical characteristics, and lipid profile in individuals with and without DM (randomized population)

	Individuals with DM (*n* = 1054)		**Individuals without DM (*n* = 2445)**	
	Alirocumab (*n* = 699)	**Placebo (*n* = 355)**	**Alirocumab (*n* = 1625)**	**Placebo (*n* = 820)**
Age, years, mean (SD)	61.7 (9.5)	60.8 (10.2)	57.3 (12.2)	57.9 (11.7)
Male, *n* (%)	405 (57.9)	192 (54.1)	1010 (62.2)	520 (63.4)
Race, white, *n* (%)	581 (83.1)	290 (81.7)	1558 (95.9)	782 (95.4)
BMI, kg/m^2, mean (SD)	32.4 (6.3)	32.9 (6.0)	29.1 (5.0)	29.2 (5.1)
ASCVD[a], *n* (%)	439 (62.8)	222 (62.5)	1176 (72.4)	612 (74.6)
CHD, *n* (%)	388 (55.5)	193 (54.4)	1066 (65.6)	573 (69.9)
ACS, *n* (%)	247 (35.3)	134 (37.7)	733 (45.1)	394 (48.0)
Coronary revascularization procedure, *n* (%)	271 (38.8)	133 (37.5)	735 (45.2)	389 (47.4)
Other clinically significant CHD[b], *n* (%)	145 (20.7)	74 (20.8)	477 (29.4)	248 (30.2)
Peripheral arterial disease, *n* (%)	32 (4.6)	23 (6.5)	65 (4.0)	33 (4.0)
Ischemic stroke, *n* (%)	60 (8.6)	26 (7.3)	139 (8.6)	60 (7.3)
HeFH, *n* (%)	85 (12.2)	55 (15.5)	753 (46.3)	364 (44.4)
High-intensity statin[c], *n* (%)	311 (44.5)	153 (43.1)	1016 (62.5)	529 (64.5)
With HeFH	63 (74.1)	42 (76.4)	600 (79.7)	294 (80.8)
Without HeFH	248 (40.4)	111 (37.0)	416 (47.7)	235 (51.5)
With ASCVD	213 (48.5)	115 (51.8)	697 (59.3)	377 (61.6)
Without ASCVD	98 (37.7)	38 (28.6)	319 (71.0)	152 (73.1)
Baseline lipids, mean (SD), mg/dL				
Calculated LDL-C	116.5 (37.6)	119.7 (41.2)	131.3 (48.9)	129.8 (45.9)
Non-HDL-C	150.0 (42.6)	151.6 (46.7)	158.1 (52.1)	157.2 (49.2)
Apo B	101.6 (26.4)	101.1 (28.0)	105.4 (30.0)	105.2 (28.7)
Lp(a), median (Q1, Q3)	21.1 (6.0, 58.0)	19.0 (5.8, 61.6)	26.0 (10.0, 73.0)	24.9 (7.5, 71.8)
Fasting TGs, median (Q1, Q3)	147.0 (108.0, 205.3)	144.0 (105.3, 205.0)	118.0 (85.0, 163.7)	120.7 (88.0, 169.0)

Table 1 continued

	Individuals with DM (n = 1054)		Individuals without DM (n = 2445)	
	Alirocumab (n = 699)	Placebo (n = 355)	Alirocumab (n = 1625)	Placebo (n = 820)
HDL-C	47.6 (11.6)	48.1 (12.3)	51.1 (13.8)	50.5 (13.2)

ACS acute coronary syndrome, *Apo* apolipoprotein, *ASCVD* atherosclerotic cardiovascular disease, *BMI* body mass index, *CHD* coronary heart disease, *DM* diabetes mellitus, *HDL-C* high-density lipoprotein cholesterol, *HeFH* heterozygous familial hypercholesterolemia, *LDL-C* low-density lipoprotein cholesterol, *Lp(a)* lipoprotein (a), *Q1, Q3* first and third quartiles, *SD* standard deviation, *TG* triglyceride

[a] Included CHD, peripheral arterial disease, and ischemic stroke; for study FH II, ischemic stroke, transient ischemic attack, carotid endarterectomy, or carotid artery stent procedure and renal artery stent procedure were also included

[b] Diagnosed by invasive or non-invasive testing

[c] High-intensity statins defined as atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg

patients received statin therapy. Baseline high-intensity statin use was lower among individuals with DM (43.1–44.5%) versus without DM (62.5–64.5%), but was greater in individuals with HeFH versus those without (74.1–80.8% vs 37.0–51.5%, respectively). In total, 48.6–61.6% of individuals with ASCVD and 28.6–73.1% of those without ASCVD received high-intensity statin at baseline (Table 1).

Overall, individuals with DM had lower baseline Lp(a) and HDL-C levels but higher TG levels than individuals without DM (Table 1).

Among individuals with DM, 27.8% were receiving injectable treatments which always consisted of insulin (27.8%), sometimes combined with a glucagon-like peptide 1 antagonist (GLP 1; 3.3%). No individuals were receiving GLP 1 antagonist only.

Efficacy

LDL-C Outcomes: Pool of Alirocumab 150 mg Q2W Studies (LONG TERM and HIGH FH)

At week 24 in the full alirocumab 150 mg Q2W cohort, the least-squares mean LDL-C levels were changed from baseline by − 59.9% (with DM; placebo, − 1.4%) and − 60.6% (without DM; placebo, + 1.5%) (Table 2). Regardless of high-intensity statin status, the LDL-C percentage change from baseline to week 24 was similar in participants with and without DM (Fig. 1). Mean week 24 LDL-C levels of 52.3 mg/dL were achieved in alirocumab-treated individuals with DM (absolute change from baseline, − 73.6 mg/dL) and 50.2 mg/dL in those without DM (absolute change from baseline, − 75.7 mg/dL). LDL-C levels < 70 mg/dL at week 24 were attained by 77.7% of alirocumab-treated individuals with DM and 76.8% of those without DM (placebo, 10.3% and 6.4%, respectively) (Table 2).

In the same alirocumab 150 mg Q2W group, least-squares mean percentage change from baseline to week 12 in LDL-C levels was − 62.1% in individuals with DM (placebo, + 0.1%) and − 62.9% in individuals without DM (placebo, + 1.7%) (Supplementary Table 1). At week 12, alirocumab-associated LDL-C changes were similar for patients with or without DM in the HeFH subgroup (DM, − 56.2%; non-DM, − 57.2%) and the non-HeFH subgroup (DM, − 62.5%; non-DM, − 65.4%) (Supplementary Tables 2 and 3). LDL-C levels were maintained through 78 weeks in individuals with and without DM in the on-treatment population (Fig. 2a). The reductions up to 78 weeks for the ITT population are presented in Supplementary Fig. 2A.

In the HeFH subjects from the LONG TERM and HIGH FH studies, least-squares mean LDL-C levels changed from baseline to week 24 by

Table 2 Change from baseline of lipids and achievement of LDL-C < 70 mg/dL at week 24 (intention-to-treat population)

	Alirocumab 150 mg Q2W pool (*n* = 2416)				Alirocumab 75/150 mg Q2W pool (*n* = 1043)			
	Individuals with DM (*n* = 836)		Individuals without DM (*n* = 1580)		Individuals with DM (*n* = 202)		Individuals without DM (*n* = 841)	
	Alirocumab (*n* = 556)	Placebo (*n* = 280)	Alirocumab (*n* = 1045)	Placebo (*n* = 535)	Alirocumab (*n* = 132)	Placebo (*n* = 70)	Alirocumab (*n* = 561)	Placebo (*n* = 280)
Calculated LDL-C, mg/dL								
Baseline, mean (SE)	117.4 (1.6)	119.1 (2.4)	130.6 (1.5)	128.7 (2.0)	112.8 (3.6)	119.8 (5.5)	133.0 (2.0)	132.5 (2.7)
Calculated LDL-C at week 24, mean (SE)	52.3 (1.5)	116.8 (2.1)	50.2 (1.1)	124.4 (1.5)	71.1 (3.5)	122.5 (4.7)	63.1 (1.6)	136.4 (2.2)
Percentage change from baseline to week 24, LS mean (SE)	− 59.9 (1.2)	− 1.4 (1.7)	− 60.6 (0.9)	1.5 (1.3)	− 43.8 (2.5)[a]	0.3 (3.4)	− 49.7 (1.6)[a]	5.1 (1.6)
Percentage difference vs placebo	− 58.5 (2.1)		− 62.1 (1.5)		− 44.0 (4.1)		− 54.8 (2.0)	
Interaction *p* value		0.1600				0.0201		
Percentage of persons achieving LDL-C < 70 mg/dL at week 24	77.7	10.3	76.8	6.4	68.3	5.9	65.8	2.8
Interaction *p* value		0.0188				0.2525		
Other lipids, mg/dL								
Apo B, baseline, mean (SE)	101.7 (1.1)	100.6 (1.7)	104.2 (1.0)	104.4 (1.3)	99.5 (2.5)	100.4 (3.4)	107.6 (1.3)	107.3 (1.6)
Percentage change from baseline to week 24, LS mean (SE)	− 49.6 (1.1)	1.1 (1.6)	− 53.5 (0.8)	0.6 (1.2)	− 34.4 (2.0)	− 0.3 (2.6)	− 41.6 (0.9)	1.3 (1.2)
Percentage difference vs placebo	− 50.7 (2.0)		− 54.1 (1.4)		− 34.0 (3.2)		− 42.9 (1.5)	
Interaction *p* value		0.1608				0.0121		
Lp(a), baseline, mean (SE)	34.9 (1.8)	34.9 (2.3)	48.4 (1.6)	46.1 (2.2)	61.2 (6.3)	54.7 (6.9)	48.4 (2.2)	47.5 (3.2)
Percentage change from baseline to week 24, adjusted mean (SE)	− 28.5 (1.2)	− 2.0 (1.8)	− 29.3 (0.9)	− 5.1 (1.2)	− 18.1 (2.4)	− 7.6 (3.2)	− 26.5 (1.1)	− 7.7 (1.5)
Percentage difference vs placebo	− 26.5 (2.1)		− 24.2 (1.5)		− 10.5 (4.0)		− 18.8 (1.9)	
Interaction *p* value		0.3861				0.0581		

Table 2 continued

	Alirocumab 150 mg Q2W pool (n = 2416)				Alirocumab 75/150 mg Q2W pool (n = 1043)			
	Individuals with DM (n = 836)		Individuals without DM (n = 1580)		Individuals with DM (n = 202)		Individuals without DM (n = 841)	
	Alirocumab (n = 556)	Placebo (n = 280)	Alirocumab (n = 1045)	Placebo (n = 535)	Alirocumab (n = 132)	Placebo (n = 70)	Alirocumab (n = 561)	Placebo (n = 280)
Non-HDL-C, baseline, mean (SE)	151.4 (1.8)	151.3 (2.7)	158.1 (1.6)	157.5 (2.2)	143.2 (3.8)	149.5 (5.9)	158.6 (2.2)	156.9 (2.8)
Percentage change from baseline to week 24, LS mean (SE)	− 49.1 (1.1)	− 0.3 (1.5)	− 52.2 (0.8)	0.8 (1.1)	− 36.0 (2.3)	2.6 (3.1)	− 43.0 (1.1)	5.2 (1.5)
Percentage difference vs placebo	− 48.8 (1.8)		− 53.0 (1.3)		− 38.7 (3.7)		− 48.2 (1.8)	
Interaction p value		0.0603				0.0218		
TGs, baseline, mean (SE)	172.1 (4.3)	163.5 (4.9)	137.8 (2.2)	144.7 (3.3)	155.5 (8.6)	148.7 (8.0)	129.0 (3.0)	122.9 (3.6)
Percentage change from baseline to week 24, adjusted mean (SE)	− 12.2 (1.4)	6.3 (2.0)	− 16.8 (1.0)	− 0.6 (1.4)	− 7.7 (2.7)	2.4 (3.6)	− 9.1 (1.2)	1.2 (1.7)
Percentage difference vs placebo	− 18.5 (2.4)		− 16.2 (1.7)		− 10.1 (4.3)		− 10.3 (2.1)	
Interaction p value		0.4319				0.9659		
HDL-C, baseline, mean (SE)	48.3 (0.5)	48.6 (0.7)	50.7 (0.4)	50.4 (0.5)	44.5 (1.1)	45.9 (1.4)	51.9 (0.7)	50.7 (0.9)
Percentage change from baseline to week 24, LS mean (SE)	2.3 (0.6)	− 1.0 (0.9)	5.1 (0.5)	− 0.1 (0.6)	5.3 (1.4)	− 2.4 (1.9)	6.9 (0.7)	− 0.7 (0.9)
Percentage difference vs placebo	3.3 (1.1)		5.1 (0.8)		7.6 (2.3)		7.5 (1.1)	
Interaction p value		0.1680				0.9692		

Apo apolipoprotein, *DM* diabetes mellitus, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *Lp(a)* lipoprotein (a), *LS* least-squares, *Q2W* every 2 weeks, *SE* standard error, *TG* triglyceride

[a] At week 12, 26.2% of subjects with DM and 36.4% of those without DM received dose increase of 75 mg Q2W to 150 mg Q2W

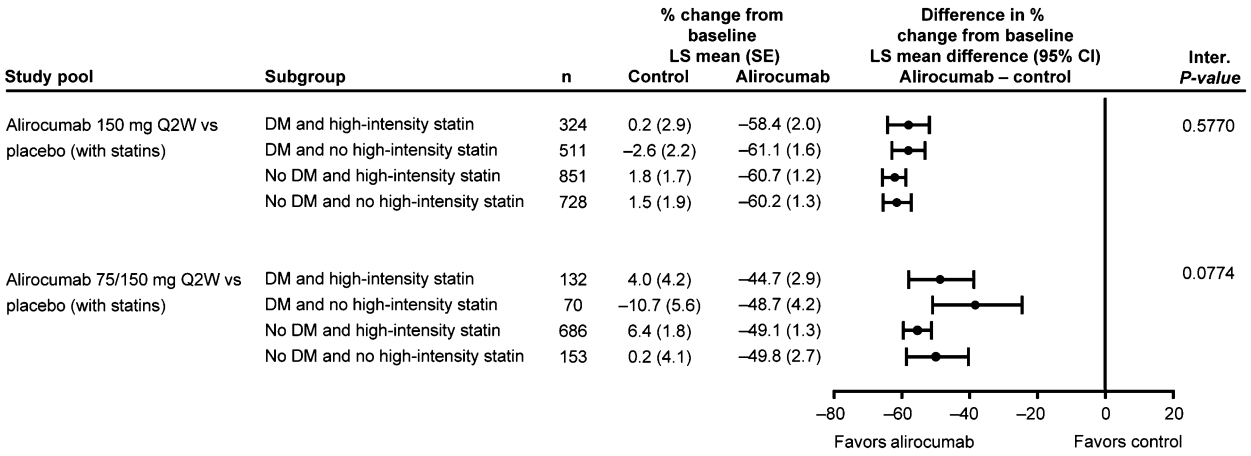


Fig. 1 Percentage change from baseline in calculated LDL-C at week 24—subgroup analysis by DM status and statin intensity at baseline (intention-to-treat population). High-intensity statin defined as atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg. *CI* confidence interval, *DM* diabetes mellitus, *LDL-C* low-density lipoprotein cholesterol, *LS* least-squares, *SE* standard error

− 53.1% (with DM; placebo, + 0.1%) and − 55.3% (without DM; placebo, + 1.5%) (Supplementary Table 4). In subjects without HeFH, the least-squares mean LDL-C changes from baseline to week 24 were − 60.3% in subjects with DM (placebo, − 1.4%) and − 62.9% in those without DM (placebo, + 1.6%) (Supplementary Table 5).

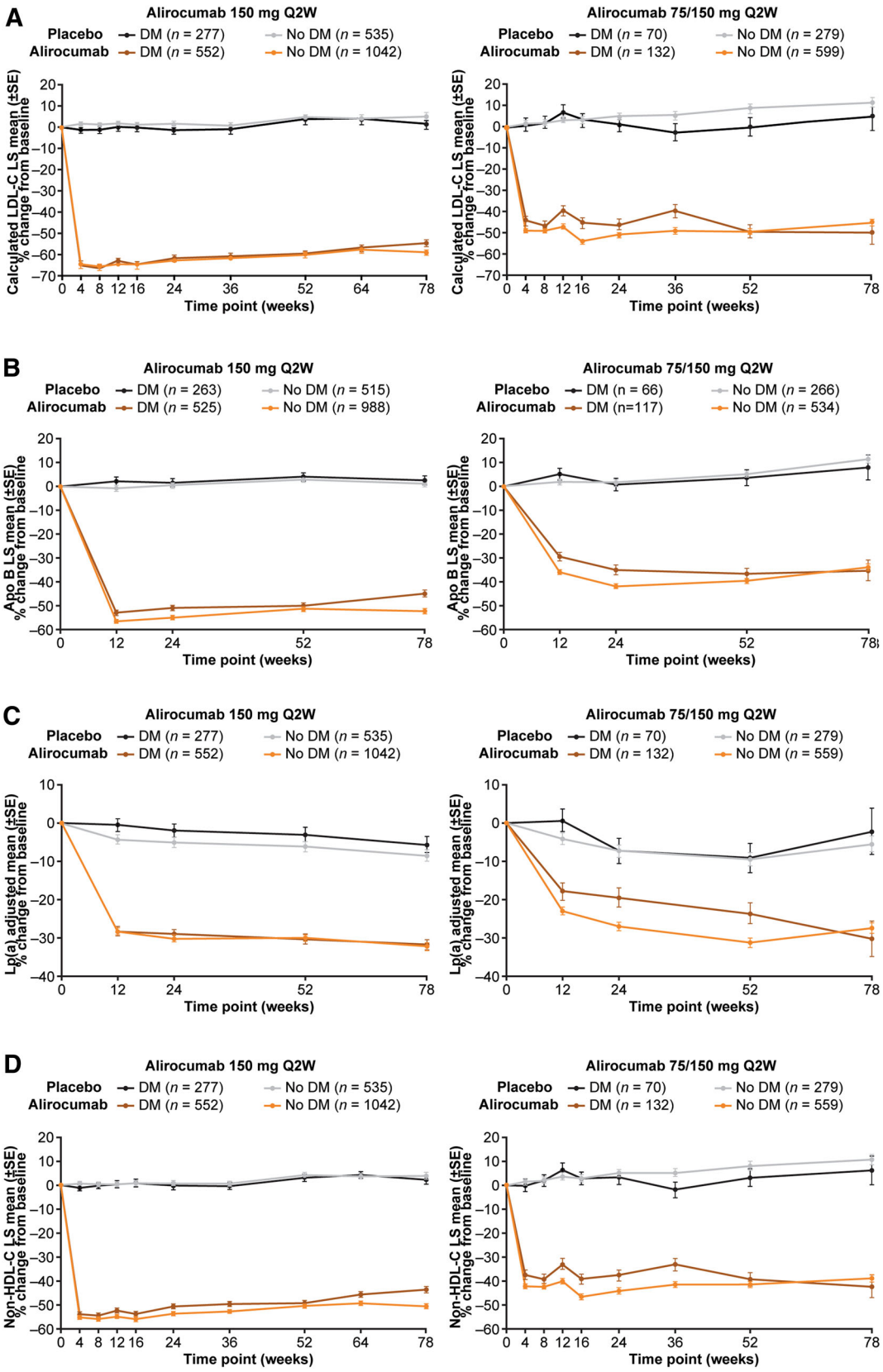
LDL-C Outcomes: Pool of Alirocumab 75/150 mg Q2W Studies (FH I, FH II, and COMBO I)

At week 24 in the full 75/150 mg Q2W cohort, least-squares mean percentage change from baseline in LDL-C level was − 43.8% (with DM; placebo, + 0.3%) and − 49.7% (without DM; placebo, + 5.1%) (Table 2). Mean week 24 LDL-C levels of 71.1 mg/dL were achieved in alirocumab-treated individuals with DM (absolute change from baseline, − 58.3 mg/dL) and 63.1 mg/dL in those without DM (absolute change from baseline, − 66.3 mg/dL). Subgroup analysis with and without high-intensity statin demonstrated similar LDL-C reductions at week 24, regardless of DM status (Fig. 1).

At week 12 in this cohort (i.e., before possible dose increase), least-squares mean percentage change from baseline to week 12 in LDL-C levels was − 38.0% in persons with DM (placebo, + 7.0%) and − 46.0% in those without DM (placebo, + 3.4%) in the alirocumab 75/150 mg Q2W treatment pool (Supplementary Table 1). When the HeFH and non-HeFH subjects in this cohort were examined separately, similar percentage reductions from baseline to week 12 were observed in alirocumab-treated groups, except for a less pronounced change in LDL-C levels in individuals with DM in the HeFH subgroup (− 34.9%; placebo, + 3.6%) (Supplementary Tables 2 and 3).

The protocol for the three studies starting with the alirocumab 75 mg Q2W dose specified a blinded dose increase from 75 mg to 150 mg Q2W at week 12 (if week 8 LDL-C levels were ≥ 70 mg/dL); 26.2% of individuals with DM received a dose increase to 150 mg Q2W, as did 36.4% of those without DM. In subjects remaining on 75 mg Q2W, the baseline LDL-C levels were lower in those with DM (99.5 mg/dL) versus subjects without DM (117.9 mg/dL; interaction p value < 0.0001). In subjects receiving alirocumab dose increase to 150 mg Q2W, the baseline LDL-C levels were 149.7 mg/dL (DM) and 159.4 mg/dL (without DM).

LDL-C reductions were maintained with alirocumab 75/150 mg Q2W until end of study treatment, regardless of DM status, in the on-treatment population (Fig. 2a). Similar LDL-C


A
Alirocumab 150 mg Q2W
Placebo DM (n = 277) No DM (n = 535)
Alirocumab DM (n = 552) No DM (n = 1042)
Calculated LDL-C LS mean (±SE) % change from baseline
Time point (weeks)
Alirocumab 75/150 mg Q2W
Placebo DM (n = 70) No DM (n = 279)
Alirocumab DM (n = 132) No DM (n = 599)
Calculated LDL-C LS mean (±SE) % change from baseline
Time point (weeks)
B
Alirocumab 150 mg Q2W
Placebo DM (n = 263) No DM (n = 515)
Alirocumab DM (n = 525) No DM (n = 988)
Apo B LS mean (±SE) % change from baseline
Time point (weeks)
Alirocumab 75/150 mg Q2W
Placebo DM (n = 66) No DM (n = 266)
Alirocumab DM (n=117) No DM (n = 534)
Apo B LS mean (±SE) % change from baseline
Time point (weeks)
C
Alirocumab 150 mg Q2W
Placebo DM (n = 277) No DM (n = 535)
Alirocumab DM (n = 552) No DM (n = 1042)
Lp(a) adjusted mean (±SE) % change from baseline
Time point (weeks)
Alirocumab 75/150 mg Q2W
Placebo DM (n = 70) No DM (n = 279)
Alirocumab DM (n = 132) No DM (n = 559)
Lp(a) adjusted mean (±SE) % change from baseline
Time point (weeks)
D
Alirocumab 150 mg Q2W
Placebo DM (n = 277) No DM (n = 535)
Alirocumab DM (n = 552) No DM (n = 1042)
Non-HDL-C LS mean (±SE) % change from baseline
Time point (weeks)
Alirocumab 75/150 mg Q2W
Placebo DM (n = 70) No DM (n = 279)
Alirocumab DM (n = 132) No DM (n = 559)
Non-HDL-C LS mean (±SE) % change from baseline
Time point (weeks)

◀**Fig. 2** Percentage change from baseline over time for **a** LDL-C, **b** Apo B, **c** Lp(a), **d** non-HDL-C, **e** TGs, and **f** HDL-C according to DM status for the alirocumab 150 mg Q2W and 75/150 mg Q2W treatment pools (modified intention-to-treat population). *Apo* apolipoprotein, *DM* diabetes mellitus, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *Lp(a)* lipoprotein (a), *LS* least-squares, *Q2W* every 2 weeks, *SE* standard error, *TG* triglyceride

reductions were observed in the ITT population (Supplementary Fig. 2a).

At week 24, LDL-C < 70 mg/dL was attained by 68.3% of individuals in the alirocumab group with DM and 65.8% without DM (placebo, 5.9% and 2.8%, respectively) (Table 2).

In the HeFH subgroup, the proportion of individuals requiring dose increase from alirocumab 75 mg to 150 mg Q2W was 48.7% (DM) and 41.2% (without DM). At week 24, least-squares mean percentage changes in LDL-C level were − 52.3% in persons with DM (placebo, + 2.7%) and − 48.4% in those without DM (placebo, + 7.6%) (Supplementary Table 4). In the non-HeFH subgroup, 16.5% of persons with DM and 17.0% of those without DM received dose adjustment at week 12. In this same group, the week 24 least-squares mean LDL-C levels changed from baseline by − 42.2% in persons with DM (placebo, − 2.6%) and − 53.2% in those without DM in the subgroup (placebo, − 2.0%) (Supplementary Table 5).

Other Lipid Parameters

From baseline to week 24, alirocumab treatment was associated with reduced levels of apolipoprotein (Apo) B, Lp(a), non-HDL-C, and TGs, and increased levels of HDL-C (Table 2). In the alirocumab 150 mg Q2W pool, no differences between subjects with and without DM were observed (Table 2). In the alirocumab 75/150 mg Q2W pool, lower percentage changes in Apo B and non-HDL-C were observed in participants with DM versus those without (interaction *P* values < 0.05) (Table 2). The

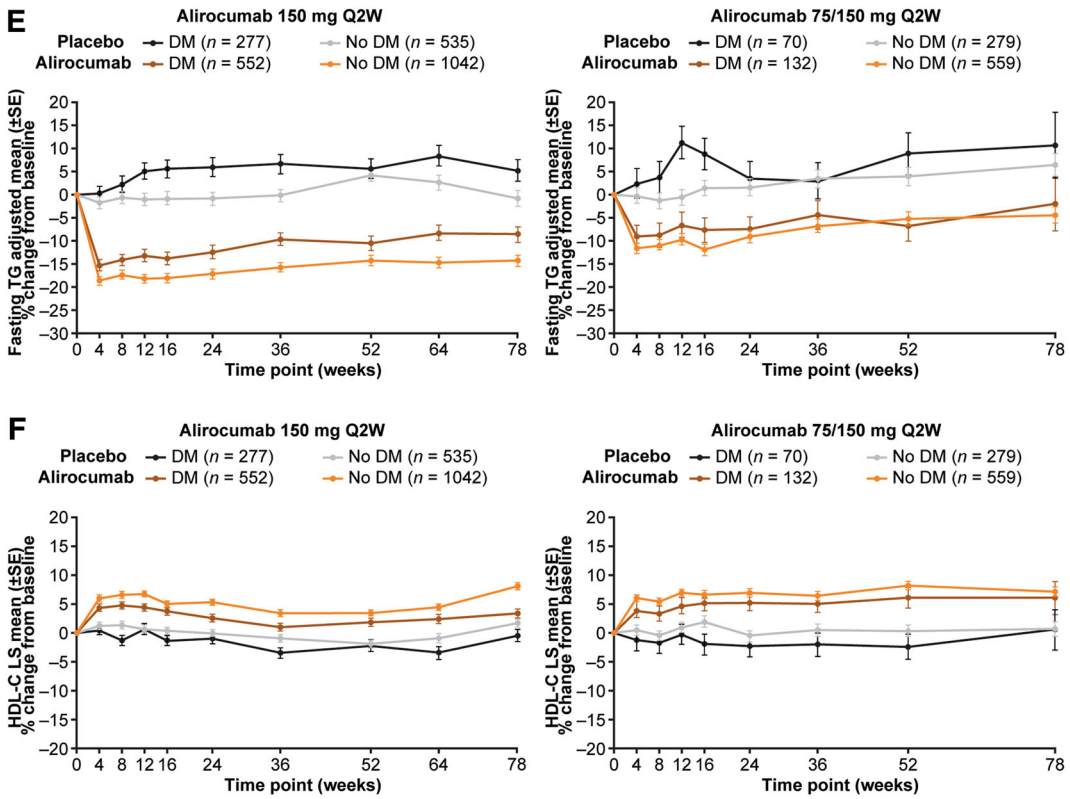


Fig. 2 continued

percentage changes in TG and HDL-C levels were similar regardless of DM status.

From baseline to week 12, alirocumab dosing regimens of 150 mg Q2W and 75/150 mg Q2W were associated with improved levels of Apo B, Lp(a), non-HDL-C, TGs, and HDL-C in subjects with or without DM (Supplementary Table 1).

In persons with and without HeFH, similar alirocumab efficacy was observed at week 12, regardless of DM status and alirocumab dosing regimen, except for lower Apo B and non-HDL-C levels in individuals with HeFH in the alirocumab 75/150 mg group with DM (interaction p value < 0.05 between persons with DM and those without) (Supplementary Tables 2 and 3).

Reduced levels of other lipids were observed from week 4 and maintained for up to 78 weeks in individuals with and without DM in the on-treatment population (Fig. 2b–f). The lipid levels for the ITT population were similar (Supplementary Fig. 2B–F). In the HeFH group, improvements in other lipids from baseline to week 24 were seen in individuals with DM and without, regardless of alirocumab dosing (Supplementary Table 4). No differences between subjects with and without DM were observed in the non-HeFH group either, except for lower mean percentage reductions in Apo B levels in subjects with DM in both alirocumab groups and lower mean percentage reductions in non-HDL-C levels in subjects with DM in the alirocumab 150 mg Q2W pool (interaction p value < 0.05 between persons with DM and those without; Supplementary Table 5).

No correlation was found between baseline HbA1c levels and LDL-C reductions in alirocumab-treated individuals with DM at week 24 (Supplementary Fig. 3).

Safety Analysis

Overall, the incidence of TEAEs was similar between groups, occurring in 79.9% with DM and 79.8% without DM in alirocumab-treated individuals versus 82.0% and 81.0% in the placebo groups, respectively (Table 3). The most common TEAEs occurring in $\geq$ 5% of individuals treated with alirocumab were nasopharyngitis, reported in 11.5% (n = 80) of individuals with DM and 13.0% (n = 211) of those without DM, and upper respiratory tract infection, reported in 7.9% (n = 55) and 6.6% (n = 107), respectively. Among alirocumab-treated individuals, 3.7% (n = 26) of those with DM and 8.7% (n = 141) of individuals without DM reported injection-site reactions (Table 3). Overall, 20.3% (alirocumab) and 23.9% (placebo) of subjects in the DM group and 15.0% (alirocumab) and 14.3% (placebo) of those without DM experienced treatment-emergent serious adverse events. Discontinuation rates were 5.6% (alirocumab) and 8.0% (placebo) in individuals with DM, and 5.4% (alirocumab) and 5.7% (placebo) in those without DM (Table 3). Occurrence of adverse events of special interest in alirocumab-treated individuals was generally similar regardless of DM status (Table 3). Overall, the median exposure to randomized treatment was 78 weeks in both the alirocumab and control groups, regardless of DM status. Mean HbA1c and FPG levels remained unchanged in both groups throughout the treatment period regardless of DM status (Supplementary Table 6).

DISCUSSION

Across all studies in the ODYSSEY program, individuals with hypercholesterolemia experienced significant LDL-C reductions from baseline compared with either placebo or ezetimibe following alirocumab treatment with background statin therapy (± other lipid-lowering therapies) [16–19]. Similar reductions were seen with alirocumab treatment in individuals with or without DM, and were maintained for up to 78 weeks.

In the present analysis, alirocumab 150 mg Q2W resulted in 58.5% and 62.1% reductions in LDL-C levels versus placebo at week 24 with no significant difference being observed between those with and those without DM, respectively. Furthermore, LDL-C levels of < 70 mg/dL were achieved by the majority of persons receiving this dose regardless of DM status (76.9–77.7%), with mean achieved LDL-C levels of 50.2–52.3 mg/dL, regardless of DM status.

Table 3 Adverse events in persons with and without DM (safety population)

n (%)	DM (*n* = 1051)		No DM (*n* = 2441)	
	Alirocumab (*n* = 696)	Placebo (*n* = 355)	Alirocumab (*n* = 1622)	Placebo (*n* = 819)
TEAEs	556 (79.9)	291 (82.0)	1295 (79.8)	663 (81.0)
Treatment-emergent SAEs	141 (20.3)	85 (23.9)	244 (15.0)	117 (14.3)
TEAEs leading to discontinuation	56 (8.0)	20 (5.6)	88 (5.4)	47 (5.7)
TEAEs leading to death	7 (1.0)	5 (1.4)	9 (0.6)	8 (1.0)
Adverse events of special interest				
HLT: injection site reactions	26 (3.7)	10 (2.8)	141 (8.7)	52 (6.3)
General allergic TEAE (CMQ)	63 (9.1)	28 (7.9)	163 (10.0)	77 (9.4)
Neurocognitive disorders	9 (1.3)	6 (1.7)	12 (0.7)	3 (0.4)
Adjudicated cardiovascular events	37 (5.3)	27 (7.6)	57 (3.5)	19 (2.3)
ALT $> 3 \times$ ULN, *n/N* (%)	11/689 (1.6)	14/349 (4.0)	34/1610 (2.1)	7/815 (0.9)
TEAEs occurring in $\geq$ 5% of persons				
Nasopharyngitis	80 (11.5)	35 (9.9)	211 (13.0)	107 (13.1)
Upper respiratory infection	55 (7.9)	36 (10.1)	107 (6.6)	58 (7.1)
Injection-site reaction	26 (3.7)	10 (2.8)	141 (8.7)	52 (6.3)
Bronchitis	33 (4.7)	27 (7.6)	79 (4.9)	31 (3.8)
Urinary tract infection	49 (7.0)	26 (7.3)	79 (4.9)	39 (4.8)
Arthralgia	27 (3.9)	26 (7.3)	91 (5.6)	50 (6.1)
Influenza	39 (5.6)	19 (5.4)	108 (6.7)	44 (5.4)
Back pain	33 (4.7)	17 (4.8)	90 (5.5)	53 (6.5)
Headache	29 (4.2)	16 (4.5)	90 (5.5)	48 (5.9)
Diarrhea	33 (4.7)	17 (4.8)	90 (5.5)	40 (4.9)
Myalgia	21 (3.0)	11 (3.1)	90 (5.5)	35 (4.3)

ALT alanine aminotransferase, *CMQ* custom MedDRA query, *DM* diabetes mellitus, *HLT* high-level term, *MedDRA* Medical Dictionary of Regulatory Activities, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event, *ULN* upper limit of normal

In the pool of studies where per-protocol dose increase from 75 mg to 150 mg Q2W occurred if LDL-C goals were not reached at week 8, the week 24 LDL-C levels from baseline were changed by − 43.8% (individuals with DM) and − 49.7% (individuals without DM) in the alirocumab groups (placebo, + 0.3% and + 5.1%, respectively), with these changes being

consistent regardless of DM status. Possibly as a result of the higher LDL-C levels at baseline, alirocumab dose was increased at week 12 in a higher proportion of subjects without DM, which was associated with a greater magnitude of LDL-C reduction at week 24 in that group (absolute LDL-C change, − 66.3 mg/dL) versus the DM group (absolute LDL-C change, − 58.3 mg/dL); however, similar LDL-C levels (63.1–71.1 mg/dL) were achieved in both groups. In the subgroup without HeFH, the percentage of individuals requiring dose increase was similar regardless of DM status. Therefore, this analysis indicates that the higher proportion of individuals in the subgroup without DM who received alirocumab dose increase versus the subgroup with DM could be explained by more individuals with HeFH with higher baseline LDL-C being included in the subgroup without DM.

At baseline, the differences in prevalence of HeFH, ASCVD, and high-intensity statin use, and baseline LDL-C levels between individuals with and without DM may reflect discrepancies in selection criteria between the studies included in the analysis. Furthermore, consistent with previous studies [21, 22], fewer individuals with HeFH had DM (12.2–15.5%) compared with those without HeFH (44.4–46.3%). Possibly as a result of this imbalance, fewer individuals in the cohort with DM had a history of ASCVD and received high-intensity statin compared with the cohort without DM. The lower rate of high-intensity statin use in individuals with DM indicates that this high-risk population is undertreated.

Overall, alirocumab treatment was generally well tolerated with no particular differences observed in incidence of TEAEs, serious adverse effects, or deaths compared with placebo in individuals with or without DM. Overall, mean exposure to randomized treatment was similar (78 weeks) in individuals with or without DM regardless of treatment status. This analysis does not allow for conclusive safety observations to be made, in particular for rare adverse events such as adjudicated cardiovascular events. As a consequence, safety results should be considered in the context of the overall ODYSSEY program.

Fewer injection-site reactions were reported in individuals with DM, a difference that may in part be due to a greater familiarity and tolerance associated with glucometer and/or injectable medication use in the DM population (27.8% and 72.2% of persons with DM were receiving antihyperglycemic injectable and non-injectable medication at baseline, respectively). However, as previously reported, administration by injection does not deter persons from self-administration of alirocumab [23]. The ODYSSEY OUTCOMES study (NCT01663402) will help to further establish if DM status has an influence on the frequency of injection-site reactions [24].

Mean HbA1c and FPG measurements in individuals with DM were comparable between alirocumab and placebo for up to 78 weeks of treatment. These variables were comparable between alirocumab and placebo in individuals without DM, as previously reported [25]. On the basis of these results, alirocumab treatment does not appear to affect blood glucose, which is very reassuring given that statins modestly raise the risk of DM [26], and recent genetic publications have suggested that the PCSK9 pathway might be relevant to glycemia levels [27, 28]. In a subgroup analysis of 11,031 individuals with DM in FOURIER (median follow-up, 2.2 years), neither HbA1c nor incidence of DM was increased in the evolocumab groups versus the placebo groups [29]. In contrast, a recent meta-analysis of phase 2/3 randomized PCSK9 inhibitor clinical studies (excluding FOURIER) suggested that PCSK9-mediated lowering of LDL-C does increase risk for DM [30]. Taking all of these publications into consideration, it is not yet clear whether LDL-C reduction per se or the means of attaining lower LDL-C levels influence DM risk. In the ODYSSEY and FOURIER studies, most individuals received statin therapy, which may mask the glycemic effect of PCSK9 inhibitors [29, 31]. The results of ODYSSEY OUTCOMES will provide key additional data relevant to this important issue.

Overall efficacy and safety findings from these placebo-controlled studies were consistent with findings from studies comparing alirocumab with ezetimibe and employing background statin therapy [32, 33]. A recently

published study of the efficacy and safety of alirocumab in individuals with type 2 DM and mixed dyslipidemia (defined as non-HDL-C $\geq$ 100 mg/dL; TGs $\geq$ 150 mg/dL and $<$ 500 mg/dL) showed similar responses for non-HDL-C (37.7% reduction) and TGs (13.0% reduction) at week 24 compared to the larger group of individuals with type 1 and 2 DM in the present analysis [15]. In the DM-INSULIN phase 3b study, alirocumab demonstrated similar results in reducing LDL-C and other lipids in insulin-treated type 1 DM and type 2 DM individuals [14]; all individuals were at high cardiovascular risk and received maximally tolerated statin therapy.

This analysis was limited by the non-randomized nature of DM status in subgroups, which could introduce bias to the analyses. Nevertheless, this placebo-controlled analysis of up to 78 weeks adds to the body of evidence on PCSK9 inhibitor use in people with DM [34].

CONCLUSION

On the basis of these data from placebo-controlled phase 3 studies, DM status does not appear to meaningfully affect lipid-modifying efficacy or safety of alirocumab treatment, nor does alirocumab appear to significantly affect blood glucose control in individuals with or without DM. The results presented here provide support for the recent recommendation by the American Diabetes Association that PCSK9 inhibitor therapy may be considered for individuals with DM and ASCVD [8]. The ODYSSEY OUTCOMES study is expected to provide an opportunity to evaluate the effect of alirocumab in a larger sample of individuals with DM [24].

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